RESEARCH LETTER

A systematic review of vitiligo onset and exacerbation in patients receiving biologic therapy

To the Editor: Biologic therapies have improved outcomes in patients with immune-mediated inflammatory diseases due to their ability to inhibit specific proinflammatory cytokines, such as tumor necrosis factor-alfa (TNF-α) and interleukins (IL).[1] An infrequent side effect of biologic therapy is the onset of vitiligo. This systematic review aimed to comprehensively summarize the existing literature on new-onset and exacerbations of vitiligo after biologic use.

Twenty-one studies were included after the OVID Embase and MEDLINE databases were systematically searched on July 13, 2020, in accordance with the PRISMA guidelines. The following search keywords were used: "vitiligo" and "specific biologics." Overall, 140 patients (mean age, 46.7 years; males, 59.5% [50 of 84 patients]) reported vitiligo-related complications while on biologics (Table I).

Of the 140 patients, 84.3% (118 patients) experienced de novo vitiligo and 15.7% (22 patients) experienced exacerbation of pre-existing vitiligo after the administration of the following reported biologics: anti−TNF-α (82.6% [71 of 86 patients]), anti-CD52 (7.0% [6 of 86 patients]), anti−IL-12/23 (4.7% [4 of 86 patients]), anti−IL-17A (2.3% [2 of 86 patients]), anti-CD20 (2.3% [2 of 86 patients]), and anti−IL-6 (1.2% [1 of 86 patients]); specific biologics were not reported in 54 patients. The most common biologic indications were: ankylosing spondylitis (29.1% [25 of 86 patients]), psoriasis (22.1% [19 of 86 patients]), and Crohn's disease (14.0% [12 of 86 patients]). Of the locations of depigmentation that the authors reported, the trunk and/or extremities (60.4% [32 of 53 patients]) were most commonly affected. The mean duration of exposure to biologics before vitiligo development or exacerbation was 13.1 months (range: 1.4-60 months).

Vitiligo treatment was reported for 31 patients, which included topical corticosteroids (22.6% [7 of 31 patients]), topical tacrolimus (19.4% [6 of 31 patients]), and a combination of excimer laser and topical tacrolimus (9.7% [3 of 31 patients]) (Table II). Complete resolution of vitiligo was observed in 4.5% of cases (2 of 44 patients) after biologic

Table I. Summary of characteristics and clinical outcomes of vitiligo in patients on biologic therapy

Characteristics	Participants
Total (n)	140
Age (y)	
Mean age ± standard deviation	46.7 ± 9.1
Age range	21-83
Reported total (n)	58
Sex (n, %)	
Female	34 (40.5)
Male	50 (59.5)
Reported total	84
Prior use of biologics (n, %)	
Yes	3 (27.3)
No	8 (72.7)
Reported total	11
Biologics (n, %)	
TNF-α inhibitor	71 (82.6)
Adalimumab	32
Infliximab	26
Etanercept	11
Certolizumab	2
CD52 inhibitor	6 (7.0)
Alemtuzumab	6
IL-12/23 inhibitor	4 (4.7)
Ustekinumab	4
IL-17A inhibitor	2 (2.3)
Secukinumab	1
Ixekizumab	1
CD20 inhibitor	1 (1.2)
Rituximab	1
IL-6 receptor inhibitor	1 (1.2)
Tocilizumab	1
CTLA-4 inhibitor	1 (1.2)
Abatacept	1
Reported Total	86
Indication (n, %)	
Ankylosing spondylitis	25 (29.1)
Psoriasis	19 (22.1)
Crohn's disease	12 (14.0)
Rheumatoid arthritis	11 (12.8)
Ulcerative colitis	6 (7.0)
Multiple sclerosis	6 (7.0)
Psoriatic arthritis	4 (4.7)
Hidradenitis suppurativa	1 (1.6)
Pan uveitis	1 (1.6)
SAPHO	1 (1.6)
Reported total	86
Vitiligo outcome (n, %)	
Induction	118 (84.3)

Continued

Table I. Cont'd

Characteristics	Participants
Exacerbation	22 (15.7)
Reported total	140
Latency period (mo)	
Mean duration ± standard deviation	13.1 ± 8.4
Duration range	1.4-60
Reported total (n)	58
Cutaneous distribution (n, %)	
Extremities	30 (38.5)
Trunk	26 (33.3)
Face	10 (12.8)
Entire body	4 (5.1)
Knees	2 (2.6)
Elbows	2 (2.6)
Groin	1 (1.3)
Neck	1 (1.3)
Leucotrichia	1 (1.3)
Poliosis	1 (1.3)
Reported total (n)	78
Drug discontinuation (n, %)	
Yes	38 (82.6)
No	8 (17.4)
Reported total	46
Treatment (n, %)	
Corticosteroids	7 (22.6)
Topical tacrolimus	6 (19.4)
Excimer laser and topical tacrolimus	3 (9.7)
Oral prednisone	2 (6.5)
Clobetasol	2 (6.5)
Secukinumab	1 (3.2)
Clindamycin	1 (3.2)
Cyclophosphamide	1 (3.2)
Calcipotriol/betamethasone dipropionate	1 (3.2)
Methotrexate	1 (3.2)
Triam	1 (3.2)
Plasma infusions	1 (3.2)
Minox	1 (3.2)
Polipodium leucotomos	1 (3.2)
Vitamin E	1 (3.2)
Topical phenylalanine	1 (3.2)
Reported total	31
Clinical outcomes (n, %)	
Complete resolution	2 (4.5)
Partial resolution	13 (29.5)
No recovery	20 (45.5)
Worsening	9 (20.5)
Reported total	44
Resolution period (mo)	
Mean duration ± standard deviation	28.6 ± 8.4
Duration range	1-32
Reported total (n)	42
Drug switches (n, %)	
Etanercept	2 (66.7)
Secukinumab	1 (33.3)
Reported total	3

Table II. Summary of outcomes and treatment regimens

Management strategies	Resolution outcome	Mean resolution period (mo)
Discontinuations only	CR: 1	12
	PR: 0	N/A
	Worsening: 0	N/A
	No resolution: 0	N/A
	Reported total: 1	
Discontinuation and treatment	CR: 0	N/A
	PR: 3	6.5
	Worsening: 0	N/A
	No resolution: 0	N/A
	Reported total: 3	
Treatment only	CR: 0	N/A
	PR: 2	6.5
	Worsening: 0	N/A
	No resolution: 1	12
	Reported total: 3	
None	CR: 0	N/A
	PR: 0	N/A
	Worsening: 0	N/A
	No resolution: 1	N/A
	Reported total: 1	
NR	CR: 1	NR
	PR: 8	32
	Worsening: 9	32
	No resolution: 18	32
	Reported total: 36	

CR, Complete resolution; *N/A*, not applicable; *NR*, no resolution; *PR*, partial resolution.

discontinuation, with a mean resolution period of 12 months. A partial resolution was achieved in 37.1% of cases (13 of 35 patients): after biologic discontinuation and treatment (3 of 13 patients), treatment only (2 of 13 patients), and biologic discontinuation only (1 of 13 patients), with the mean resolution period of 6.5 months; the treatment and biologic discontinuation regimen for partial resolution in 22 patients were not reported. Additionally, 3 patients switched to an alternate biologic for their primary indication: etanercept (n = 2) and secukinumab (n = 1); no vitiligo-related adverse events were reported after the switch.

In patients that experienced vitiligo development or exacerbations, the most common biologic class was anti−TNF-α. A retrospective study documented a 2-fold increased risk of developing vitiligo among patients on anti−TNF-α as compared to the general population.[2] Long-term TNF-α inhibition may give rise to cytokine shifts and the subsequent recruitment of autoreactive T cells to the epidermis, leading

to the destruction of melanocytes.[3,4] In addition to being an adverse effect of biologics, vitiligo development or exacerbation can also be seen as a cutaneous manifestation incidentally associated with chronic immune-mediated inflammatory diseases. For instance, Snook et al[5] reported vitiligo in 1.1% of adults with ulcerative colitis and 0.5% of patients with Crohn's disease compared with 0.3% in the control population.

Limitations of this review include a small sample size, observational nature of the studies, and a mean Naranjo score of 3 (possible). Despite the need for further studies, our systematic review demonstrates that vitiligo-related complications can be associated with biologic use, especially anti−TNF-α.

Muskaan Sachdeva, BHSc,[a] Asfandyar Mufti, MD,[b] Nadia Kashetsky, MSc,[c] Jorge R. Georgakopoulos, MD,[b] Sheida Naderi-Azad, BSc,[a] Jennifer Salsberg, MD, FRCPC,[a,b,e] and Jensen Yeung, MD, FRCPC[a,b,d,e,f]

From the Faculty of Medicine[a] and Division of Dermatology, Department of Medicine, University of Toronto, Ontario, Canada,[b] Faculty of Medicine, Memorial University, St. John's, Newfoundland and Labrador, Canada,[c] Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada,[d] Women's College Hospital, Toronto, Ontario, Canada,[e] and Probity Medical Research Inc., Waterloo, Ontario, Canada.[f]

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Correspondence to: Jensen Yeung, MD, FRCPC, Women's College Hospital, Division of Dermatology, 76 Grenville St, 5th floor, Toronto, ON M5S 1B2, Canada

E-mail: jensen.yeung@utoronto.ca

REFERENCES

1. Rider P, Carmi Y, Cohen I. Biologics for targeting inflammatory cytokines, clinical uses, and limitations. *Int J Cell Biol*. 2016; 2016:1-11.
2. Bae JM, Kim M, Lee HH, et al. Increased risk of vitiligo following anti-tumor necrosis factor therapy: a 10-year population-based cohort study. *J Invest Dermatol*. 2018;138(4):768-774.
3. Palucka AK, Blanck JP, Bennett L, Pascual V, Banchereau J. Cross-regulation of TNF and IFN-α in autoimmune diseases. *Proc Natl Acad Sci U S A*. 2005;102(9):3372-3377.
4. Silva LC, Ortigosa LC, Benard G. Anti-TNF-α agents in the treatment of immune-mediated inflammatory diseases: mechanisms of action and pitfalls. *Immunotherapy*. 2010;2(6): 817-833.
5. Snook JA, De Silva HJ, Jewell DP. The association of autoimmune disorders with inflammatory bowel disease. *QJM*. 1989; 72(3):835-840.

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